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Treatment of Shock Caused by Bacterial Infections

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Bacteremia caused by Gram-negative enteric organisms accounts for the majority of instances of shock complicating bacterial infection. Control of the infection and maintenance of normal blood volume constitute the primary considerations in immediate treatment. The use of three or four doses of corticosteroid agent over a period of 24 hours is regarded as advantageous for routine treatment. Conservative and selective use of isoproterenol and phentolamine are justified for management of patients who do not respond to the administration of bactericidal drugs and volume repletion. Levarterenol and metaraminol are rarely indicated. Intravascular coagulation complicated by bleeding diathesis may serve as an indication for anticoagulation.

With more effective management of the hemodynamic defects, patients are now more likely to survive the shock state only to develop a fatal form of pulmonary failure which is yet poorly understood. Close attention to respiratory management is therefore advised.

WHEN CIRCULATORY SHOCK occurs as a complication of a severe infection, the condition is described as septic shock. Gram-negative enteric bacilli (Table 1) account for a majority of cases of bacterial shock. However, Gram-positive cocci, including the pneumococci, Staphylococcus aureus and Streptococcus hemolyticus, are the causes of infections which account for bacterial shock in a minority of cases. In addition, systemic infection due to meningococci, Clostridia and infections caused by organisms other than bacteria, including viruses, Rickettsia, and fungi are occasionally complicated by shock.

In this review, our primary focus is on the pathophysiologic and clinical features and the rationale of treatment of shock when it occurs as a complication of systemic infection due to Gram-negative enteric organisms. Both the age and the sex of the patient play important parts. Bacteremia is very rarely complicated by shock before the age of 40 except in young women during pregnancy or in infants in the neonatal period. If patients with septic abortion are excluded, the condition is approximately twice as frequent in men as in women. This reflects the higher incidence of urinary tract infection primarily due to diseases of the prostate

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TABLE 1.—*Gram-Negative Species of Enteric Bacilli Which Most Commonly Cause Bacterial Shock*

Escherichia coli
Aerobacter-Klebsiella (Aerobacter aerogenes, Klebsiella pneumonia-Friedlander)
Proteus
Paracolon bacilli
Pseudomonas pyocyanea
Salmonella

gland in older men. Diabetes, chronic liver disease, and blood dyscrasias predispose to bacteremia and shock.[1]

In most patients, a traumatic event, especially instrumentation, initiates bacteremia and shock. Surgical operation or instrumentation of the genitourinary tract is the most common cause. Other causes include operation on the gastrointestinal tract, severe burns, and manipulation of infected wounds. A disproportionately high incidence of Gram-negative sepsis also is observed in patients who receive immunosuppressive drugs, radiotherapy and prolonged treatment with antimetabolites for the management of neoplastic diseases. Prolonged treatment with corticosteroid hormones also predisposes to bacteremia and shock.[1,2]

Pathophysiology

The mechanisms which account for shock as a complication of infection reflect the biological difference between the causative organisms.[3] The specific bacteriological cause of the infection is therefore a primary consideration not only for purposes of antimicrobial therapy but also for better understanding of the mechanism of shock and its management in an individual case.[4]

In shock states caused by Gram-positive organisms, Rickettsia and viruses, vascular permeability is often increased so that there is a loss of fluid from the intravascular compartment. This, together with vasodilation as part of an inflammatory response involving the arterial resistance vessels, accounts for hypotension.

When shock occurs as a complication of bacteremia due to Gram-negative enteric bacteria, a more complex sequence of disturbances is involved. The patient may present with hypotension and warm extremities, the so-called interval of "hot shock." Arterial vasodilation usually occurs during the pyrogenic phase of the infection together with a pronounced increase in body temperature, hyperventilation with an element of respiratory alkalosis, and an increase in pulse pressure and cardiac output.[5-7] This is followed by clinical changes that are more typical of shock states, including cold extremities, oliguria, and arterial vasoconstriction with a relatively small pulse pressure. The cardiac output is reduced and the peripheral arterial resistance is usually increased.

The heart does not appear to be at fault. The best explanation for bacterial shock caused by Gram-negative enteric organisms is a redistribution of the blood volume. A substantial portion of the total volume appears to be pooled in the venous capacitance bed and hence the "effective circulating blood volume" is decreased. This results in a reduction in the volume of blood returned to the heart and, consequently, the lowering of cardiac output. Clinical signs of perfusion failure appear, including decreased mental alertness and stupor due to decreased cerebral blood flow, oliguria due to decreased renal blood flow, and cool and sometimes cyanotic skin particularly in the extremities, the tip of the nose and the ear lobes due to a reduction in skin blood flow. The blood pH is reduced and lactic acid accumulates in tissues and fluid spaces because the blood flow to muscle and viscera is not sufficient for support of normal aerobic metabolism.[3,4]

In experimental animals, shock may be induced by the injection of purified endotoxin which is a protein lipopolysaccharide complex extracted from Gram-negative organisms. It is the polysaccharide component of endotoxin that is the probable cause of the hemodynamic disturbance.

More recently, intravascular coagulation has been implicated as part of the shock syndrome. The extent to which this represents a specific phenomenon due to the action of the polysaccharide or whether it is largely due to the stagnation which occurs when blood flow is greatly reduced, is not yet clear.

Clinical Features

Typically, bacteremia due to Gram-negative enteric bacteria is heralded by a shaking chill followed by a rapid rise in temperature to levels exceeding 39°C (102.2°F). These events most often occur between two and 24 hours after pelvic surgical procedures or mechanical manipulation of the genitourinary tract. Because the skin is warm and dry during the early stage of shock, the physician may not suspect that the blood pressure has fallen. An early clue to shock may be the relatively abrupt alteration in personality and in-

appropriate behavior due to a reduction in cerebral blood flow. The cause becomes apparent as soon as the patient's blood pressure is ascertained. In a series of 169 cases of bacterial shock, the average arterial pressure fell from 138/78 to 70/36 mm of mercury.[1] As the hemodynamic defect becomes more profound, the skin becomes pale, cool and moist. Approximately one half of the patients present with gastrointestinal signs, including hyperperistalsis followed by vomiting and diarrhea, often with green and sometimes bloody stools with a characteristic "laundry room" odor.

A typical laboratory finding during the very early stages of shock is an abrupt reduction in the white blood cell count with primary reduction in the polymorphonuclear cells. Later, there is an overall increase in white cells usually to levels exceeding 20,000 cells per cubic centimeter with a decided rise in polymorphonuclear cells. Increases in serum glutamic oxalic transaminase, serum glutamic pyruvic transminase, and lactic dehydrogenase reflect cellular injury due to perfusion failure. Elevation of blood sugar reflects secretion of increased amounts of catecholamines from the adrenal medulla. Since urine flow is decreased, the renal clearance of amylase also is reduced and serum amylase may be considerably elevated in the absence of pancreatic injury. The electrocardiographic findings must be interpreted with great caution since T wave and ST segment abnormalities are not unusual in older patients after the onset of shock regardless of cause. These electrocardiographic changes are especially pronounced in patients who have coexisting coronary artery disease.

Rationale of Management

The prompt administration of antibiotics and attention to the hemodynamic status of the patient during the interval of decompensation constitute the primary aims of treatment.[8]

Selection of Antibiotic

The period from onset of shock until death is short, typically less than 48 hours. This interval has important therapeutic implications. Appropriate antibiotic treatment may triple the chances for survival.[1] However, the opportunity for such benefit will be missed if the clinician awaits the results of sensitivity studies before initiating antibiotic therapy. In instances in which pre-existing infection in the urinary tract, a wound, or another site has been recognized and the organism previously recovered, it may be reasonably assumed that the same organism accounts for bacteremia. When the results of *in vitro* antibiotic sensitivity studies on such organisms are available, antibiotics are best selected accordingly.[3]

Bacterial populations and the spectrum of antibiotic sensitivities vary from hospital to hospital and change over time within the same hospital environment. Antibiotic sensitivity tests are helpful, not only for the individual patient but also to characterize the spectrum of bacterial sensitivity in a particular institution. Before an antibiotic is administered to a patient, three specimens of blood for culture should be taken in sequence with a single vein puncture or from the central venous catheter. The specimens are labeled 1, 2, and 3. This identification is helpful since the first specimen is more likely to contain a contaminant if organisms are not recovered from the second and third samples. Antibiotic treatment is then begun on an empirical basis.

Corticosteroid Drugs

In some situations, bactericidal drugs may potentiate shock when large amounts of endotoxin are liberated from the cell wall of the dead bacteria. There is evidence that such deterimental effects of endotoxins may be prevented by the administration of pharmacological doses of corticosteroids together with the antibiotic.[2] In these circumstances, the corticosteroid acts as a drug rather than as hormone replacement since adrenal cortical insufficiency has not been demonstrated to be the cause of the shock state. Corticosteroids, in amounts which may be 50 times greater than those required for adrenal replacement, suppress systemic reactions to endotoxin, control fever, and tend to prevent the nonspecific injury of cell structures. They also increase cardiac output and decrease peripheral arterial resistance. These effects are directly opposite to the hemodynamic defects that are observed during bacterial shock in patients and in some experimental animals following the administration of the bacterial endotoxin.

Significantly higher survival has been reported by us in patients who received large doses of synthetic corticosteroid drugs.[1,9] Similar observations were made by Christy,[10] Melnick,[11] and Motsay.[12] However, the present use of this therapy is based on extrapolations from animal experiments and retrospective comparisons of survival of patients treated with and without corticosteroids. In the absence of controlled studies, the therapeutic effi-

cacy of costicosteroid analogs for treatment of patients with bacterial shock is not proven.

Volume Expansion

Considerable quantities of fluid often are sequestered at a site of inflammation or are lost because of fever, vomiting, or diarrhea. Since shock is greatly intensified when intravascular volume is depleted, fluid replacement may be an important component of therapy. Monitoring of the central venous pressure with a catheter in the vena cava or right atrium is most helpful for judging the capacity of the heart to handle the volumes of fluid which are administered.[13] If the central venous pressure is not in excess of 16 cm of water, fluid therapy is best attempted. The response to fluid may be judged from state of mental awareness, blood pressure, urine output, measurement of arterial blood pH, PCO_2, and PO_2 and measurement of changes in the central venous pressure. A rise in central venous pressure of more than 5 cm of water in response to a fluid challenge of 100 ml suggests that the heart is unable to handle additional fluid loads.

With the availability of flow-directed pulmonary artery catheters which may be inserted at the bedside without fluoroscopic control, the clinician is provided with a practical means for routine monitoring of pulmonary artery and wedged pulmonary artery pressures.[14] These measurements and especially wedged pulmonary artery pressure or pulmonary diastolic pressure constitute more precise and reliable indicators of left atrial and left ventricular filling pressure. Sudden increases in wedged pulmonary artery pressure or pulmonary diastolic pressure of more than 8 mm of mercury, or increases to levels exceeding 22 mm of mercury during volume loading, reflect critical levels of left ventricular competence. Even when the blood volume is not reduced, the infusion of fluids usually improves cardiac output as long as the pulmonary or central venous pressures do not indicate overload.

A 5 percent solution of normal human albumin is an ideal volume expander. Whole blood should be administered only when indicated. Our group favors a combination of isotonic sodium chloride with 5 percent normal human serum albumin, USP or plasma protein fraction, USP. While macromolecular dextrans (molecular weight 70,000 to 80,000) gelatin solutions, and hydroxyethyl starches (polymers of sorghum corn starch) have been employed as volume expanders, we do not favor their routine use because of adverse reactions, including increased risk of defects in blood clotting, interference with subsequent crossmatch of blood, and hypersensitivity reactions.

Alkalinization

Although acidosis frequently accompanies bacterial shock, the rationale of administering sodium bicarbonate for its reversal is questioned. Acidosis is due to failure of effective tissue perfusion rather than to a deficit of sodium ion. However, for purposes of cardiac resuscitation, reversal of metabolic acidosis by administration of between 40 and 160 mEq of sodium bicarbonate may be warranted, but effects on blood pH and osmolality should be monitored.[15]

Anticoagulation

There is justification for the administration of heparin to patients who present with signs of gross bleeding due to consumption coagulapathy, presumably due to intravascular coagulation. This treatment should be reserved for the exceptional case. It is a relatively more common complication during meningococcemia.[16]

Vasopressor and Vasodilator Drugs

The effectiveness of various vasoactive drugs for the treatment of bacterial shock has been critically examined, and particularly the indications for the use of vasopressor agents. There is general agreement that neither levarterenol (Levophed®) nor metaraminol (Aramine®) is indicated for routine treatment. To the contrary, there is evidence that they increase peripheral vasoconstriction and further compromise effective blood flow. In instances in which there is concurrent myocardial failure due to coronary insufficiency, there may be an indication for temporary increase in perfusion pressure and consequent increase in coronary blood flow. However, the effectiveness of their use even for this purpose is not fully established.

If the signs of peripheral vasoconstriction are not improved by the use of volume expanders, the possibility that isoproterenol (Isuprel®), a beta adrenergic stimulant, or alpha adrenergic blocking agents such as phenoxybenzamine (Dibenzyline®) or phentolamine (Regitine®), which serve to dilate arterial vessels, might be effective has been investigated with some promising results. Phenoxybenzamine is not currently available as an approved drug. Isoproterenol, which is a

TABLE 2.—*Suggested Doses of Antimicrobial Agents with Adjustments for Patients with Renal Failure**

Agent	*Loading dose*	*Subsequent single dose, interval, and route*	*Adjusted interval between single doses*	
			Anuria†	*Uremia‡*
Gentamycin sulfate	2.5 mg/kg	1.5 mg/kg, q 8 h, I.M.	3-4 days	2 days
Kanamycin sulfate	7.5 mg/kg	2.5 mg/kg, q 6 h, I.M.	3-4 days	2 days
Streptomycin	15 mg/kg	7.5 mg/kg, q 6 h, I.M.	3-4 days	2 days
Colistimethate sodium	5 mg/kg	2.5 mg/kg, q 12 h, I.M.	3-4 days	2 days
Polymyxin B sulfate	2.5 mg/kg	0.6 mg/kg, q 6 h, I.M.	3-4 days	2 days
Tetracycline	1.0 gm	0.25 gm, q 4 h, I.V.	3-4 days	2 days
Chloramphenicol	1.0 gm	0.5 gm§, q 4 h, I.V.	6 hours	6 hours
Ampicillin	2.0 gm	1.0 gm, q 4 h, I.V.	12 hours	6 hours
Cephalothin sodium	3.0 gm	1.5 gm, q 4 h, I.V.	24 hours	12 hours

*Modified from Barnett and Sanford.[8]
†Creatinine clearance less than or equal to 10 ml/minute.
‡Creatinine clearance greater than 10 ml/minute.
§Reduce dose in patients with severe liver disease.
I.M. = deep intramuscular injection.
I.V. = slow intravenous injection or infusion over 3 to 15 minutes.

potent cardiac stimulant, also carries the potential risk of tachycardia and cardiac arrhythmias. Both drugs may cause further decline in blood pressure. However, with progressive perfusion failure, the temporary use of these agents may be justified. We prefer the use of phentolamine inasmuch as isoproterenol acts not only as a cardiac but as a more general metabolic stimulant. It thereby increases the demands for tissue oxygen and hence the need for increased blood flow at the very time when blood flow is already markedly curtailed. In instances of congestive heart failure, and particularly when this is elicited by a fluid challenge, there is good indication for the administration of cardiac glycosides, either lanatoside (Cedilanid®) or digoxin (Lanoxin®).

General

The more general principles of immediate care inherent in the "VIP" approach to the bedside management of shock—that is, ventilation, infusion, and pumping—are advised.[17] Initial and continuing attention to ventilation is an essential part of routine treatment since more effective management often permits the patient to survive shock only to succumb subsequently to respiratory failure, the so-called "shock lung" syndrome.

In the management of bacterial shock, surgical treatment may be indicated for control of the bacterial infection. It is essential that abcesses be promptly drained and that grossly infected tissues be removed. For instance, hysterectomy may be life-saving in instances of shock complicating septic abortion, and surgical drainage of a large intraabdominal abscess is essential if antibiotics are to control the infection.

Specific Management

Antibiotics

For empirical therapy, gentamycin (Garamycin®) is now the drug of choice in our center. It is administered by intramuscular injection in amounts of 1.5 mg per kg of body weight every eight hours. On the basis of *in vitro* studies, it is effective against more than 90 percent of common strains of Gram-negative enteric organisms with the exception of proteus species, for which *in vitro* sensitivity is approximately 75 percent. This bactericidal agent has both vestibular and ototoxicity, especially when there is concurrent renal failure. Its nephrotoxicity is probably a lesser problem. Gentamycin is also highly effective against Staphylococcus aureus and therefore provides a special advantage, especially when Gram-negative enteric and staphylococcus infections coexist. Kanamycin (Kantrex®) is the drug of second choice. After a loading dose of 7.5 mg per kg of body weight, 2.5 mg per kg may be administered by deep intramuscular injection at six-hour intervals. We do not currently advise the use of these agents by the intravenous route.

When urine output is reduced to less than 800 ml a day, the dose of both gentamycin and kanamycin are correspondingly reduced. If urine output is 400 ml per 24 hours or less, the dose is reduced to one half, and if the urine output is 200 ml per 24 hours, the dosage is reduced to one fourth of the standard dose. For the use of these and other commonly used antibiotics for treatment of patients who have chronic renal disease, additional guidelines are provided in Table 2.[5,18]

In instances in which gentamycin is administered,

no additional agent is usually indicated. However, kanamycin is preferably used together with chloramphenicol (Chloromycetin®) during the interval before results of bacterial studies are available. Chloramphenicol is administered in amounts of 1.0 gram diluted in 50 ml of saline solution and is injected into a central vein over a period of three to fifteen minutes. A dose of 1.0 gram is repeated every six hours. As an alternative to chloramphenicol, cephalothin (Keflin®) may be infused intravenously in amounts of 1.5 gram every four hours.

If the infecting organism is known to be a penicillin-sensitive Proteus species, or if there is a concomitant infection with Gram-positive organisms, we advise ampicillin in amounts ranging from 6 to 12 grams per day. Penicillin administered by intravenous infusion in a dose of 12.5 grams (20 million units) daily may also be employed. In patients with acute renal failure, the sodium salt is preferred, since each one million units of potassium penicillin contains 1.67 mEq of potassium.

In infections due to Pseudomonas, a new semisynthetic penicillin, carbenicillin, is likely to be effective following infusion of between 20 and 40 grams per day. Infections due to klebsiella aerobacter which are resistant to kanamycin and chloramphenicol may be treated with intramuscular injections of colistimethate (Coly-Mycin®) or polymixin B (Aerosporin®) in amounts shown in Table 2. However, gentamycin is usually very effective. The use of tetracycline drugs, which are bacteriostatic, is reserved for instances in which there is clear superiority over bactericidal agents on the basis of *in vitro* sensitivity studies.

The administration of antibiotics one or two days before instrumentation or surgical operation has proven relatively ineffective in preventing bacteremia in shock patients with low grade urinary tract infections. We prefer that antibiotics be withheld for a period of one week before operation. If this is not feasible, soluble chemotherapeutic drugs such as sulfonamide or nitrofuran may be used before operation, but antibiotics should be withheld until specific indication arises.

Corticosteroid Agents

Potent synthetic cortisone analogs are selected since animal experiments reveal lesser toxicity when these steroids are administered in massive doses. An initial intravenous injection of dexamethasone phosphate (Decadron®) in an amount of 40 mg, is followed by injections of 20 mg at intervals of four to six hours. In most cases, only three or four injections are needed. Methylprednisolone succinate (Solu-Medrol®) may be used instead in a dose of 200 mg followed by doses of 100 mg at four-hour to six-hour intervals. Lillehei recommends even higher doses, namely 6 mg per kg of dexamethasone and 30 mg per kg of methylprednisolone.[19] However, we are not aware of objective data demonstrating increased therapeutic efficacy with these larger doses. Treatment is stopped abruptly once shock has been reversed. Suppression of adrenal cortical function is not a problem when treatment is limited to a one or two day period and no weaning is required. Hemorrhage from the upper gastrointestinal tract is a specific and not infrequent complication of this type of therapy and corticosteroid treatment should be immediately discontinued if there is evidence of bleeding from the upper gastrointestinal tract.

Vasoactive Drugs

The so-called vasopressor drugs should be used rarely and judiciously when cardiac complications supervene and only in doses which raise blood pressure just enough to maintain urine flow, preserve mentation and minimize electrocardiographic evidence of myocardial ischemia. The desirable blood pressure level is usually 20 to 30 mm below "normal" systolic pressure. The preferred pressor drug is metaraminol (Aramine). Since excessive vasoconstriction may further compromise effective blood flow and increases the workload on the heart, care is taken to minimize dosage.

Metaraminol is used in amounts of 200 to 500 mg diluted in one liter of physiological salt solution or 5 percent glucose. It is administered by continuous intravenous infusion. Although metaraminol is preferred because it causes no local ischemic injury to tissues if the needle or catheter is dislodged from a vein, levarterenol may be employed with almost equal safety in amounts of 16 mg per liter of fluid, provided 10 mg of phentolamine mesylate (Regitine) is added to each liter of fluid.

When other measures fail, a cautious trial of isoproterenol hydrochloride (Isuprel) may be justified after care has been taken to assure volume repletion. A striking increase in cardiac output is often observed during infusion of between 0.20 and 25 micrograms of isoproterenol per minute. We prefer phentolamine for these purposes after volume has been expanded and particularly in in-

stances in which clinical signs of severe vasoconstriction are unaltered by more routine treatment. Phentolamine may be infused in amounts ranging from 0.1 to 2 mg per minute over a period of 20 minutes. Following infusion of phentolamine, a decline in blood pressure may be promptly reversed by administration of additional quantities of fluid, preferably equal parts of 5 percent human serum albumin and physiological salt solution.

Adjunctive Treatment

Fever may be controlled with a cooling blanket. However, there is no evidence that depression of temperature to subnormal levels is advantageous. Chilling should be avoided, since it greatly increases the requirements for oxygen. Close attention to respiratory function is mandatory. In addition to the routine use of oxygen, the physician should be prepared to institute endotracheal intubation, mechanical ventilation, and tracheostomy. For treatment of intravascular coagulation, 5,000 international units of heparin is injected intravenously every four hours, guided by periodic measurements of blood clotting.

Conclusions

Bacteremia caused by Gram-negative enteric organisms accounts for the majority of instances of shock complicating bacterial infection. Control of the infection and maintenance of normal blood volume constitute the primary considerations in immediate treatment. The use of three or four doses of corticosteroid agent over a period of 24 hours is regarded by our group as advantageous for routine treatment. Conservative and selective use of isoproterenol and phentolamine are justified for management of patients who do not respond to the administration of bactericidal drugs and volume repletion. Levarterenol and metaraminol are rarely indicated. Intravascular coagulation complicated by bleeding diathesis may serve as an indication for anticoagulation. With more effective management of the hemodynamic defects, patients are now more likely to survive the shock state only to develop a fatal form of pulmonary failure which as yet is poorly understood. Close attention to respiratory management is therefore advised.

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